Lecture 2
States of matter

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The Liquid State

General properties

Liquefaction of gases

Vapor pressure of liquids

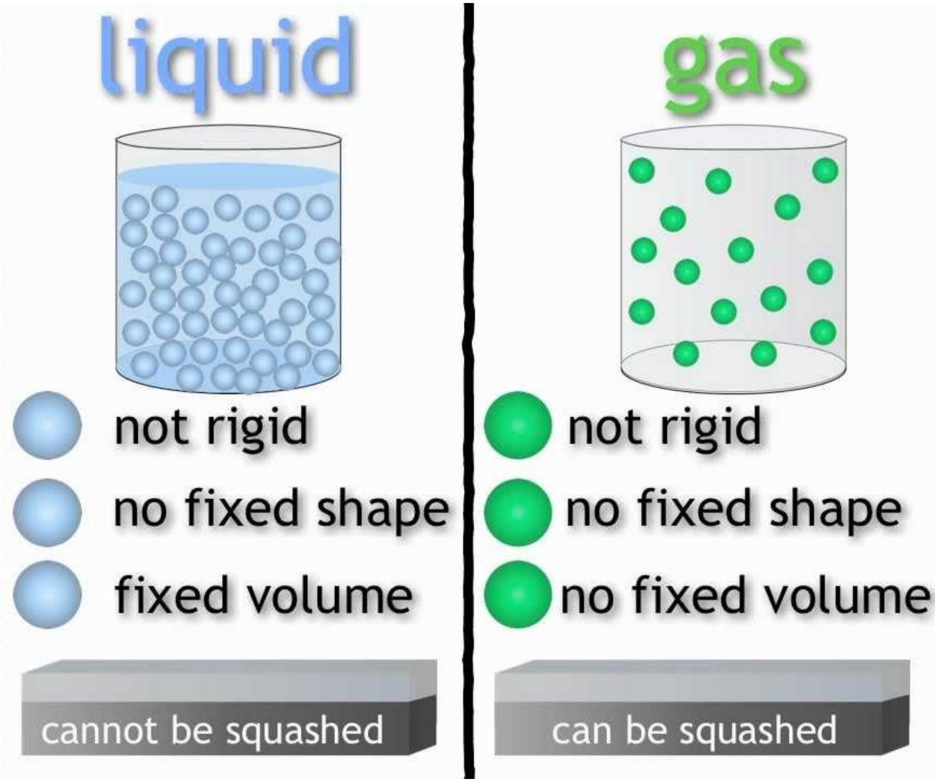
Boiling point

General properties

Liquids are denser than gases and occupy a definite volume and density due to the presence of van der Waals forces.

Liquids are relatively incompressible.

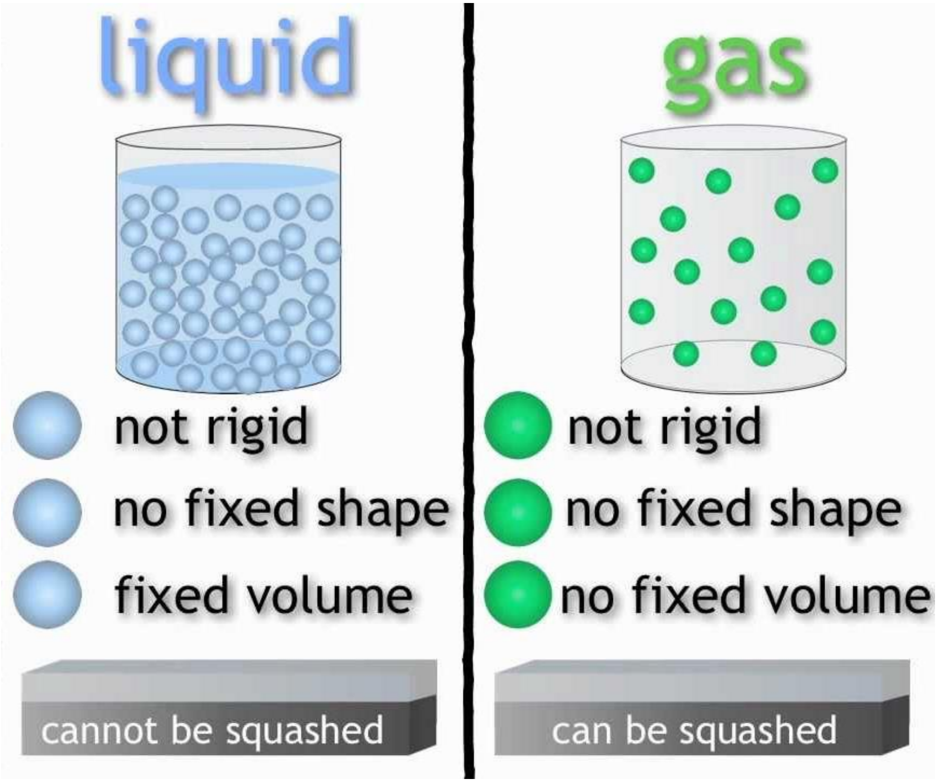
Liquid are fluids (have no definite shape) like gases.



General properties

Unlike gases, liquids do not disperse to fill all the space of a container.

Liquids have *translational motion* i.e. liquids move as a whole (the molecules can slide over each other but they cannot break away from the intermolecular forces while in the liquid state).



Liquefaction of gases

Effect of temperature and pressure

The transitions from a gas to a liquid and from a liquid to a solid depend on both temperature and pressure.

When a gas is cooled, it loses some of its kinetic energy and the velocity of the molecules decreases.

If pressure is applied to the gas, the molecules are brought within the range of the van der Waals forces and pass into the liquid state.

Q/ how can you liquefy a gas?

Liquefaction of gases

Critical temperature and pressure

Critical temperature is the temperature above which it is impossible to liquefy a gas regardless of the pressure applied.

Critical pressure is the pressure required to liquefy a gas at its critical temperature .

The further a gas is cooled below its critical temperature, the less pressure is required to liquefy it. **Why?**

Liquefaction of gases

Critical temperature and pressure

The critical temperature and pressure of water is 374 °C (647 K) and 218 atm respectively, whereas the corresponding values for helium are 5.2 K and 2.26 atm.

The high critical values for water result from the strong hydrogen bonding between the molecules.

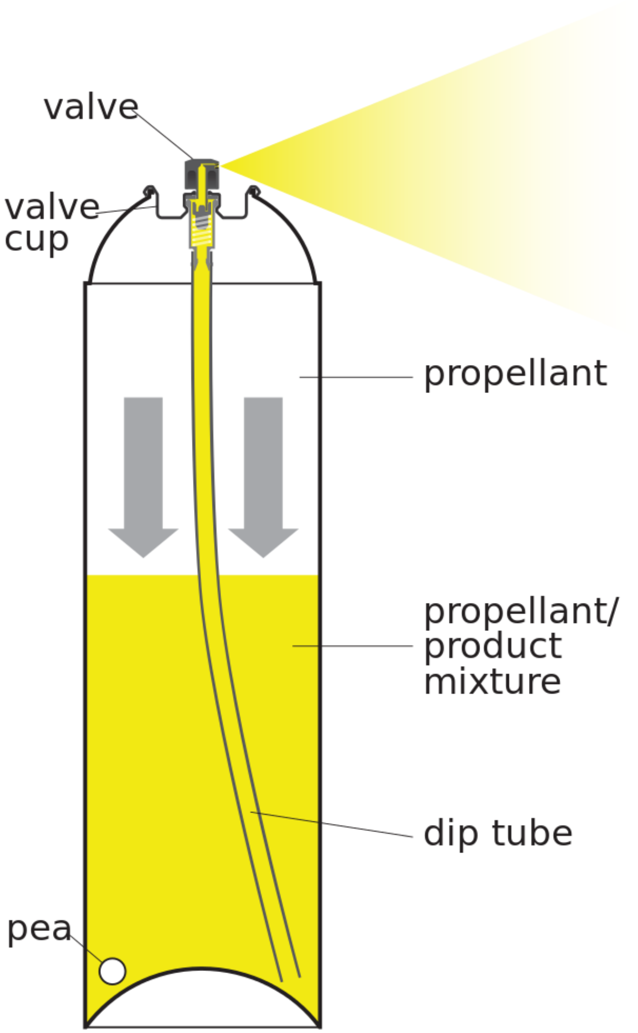
Conversely, helium molecules are only attracted by the weak London forces, and therefore; must be cooled to the extremely low temperature of 5.2 K before it can be liquefied. Above this critical temperature, helium remains a gas no matter what the pressure.

Liquefaction of gases

Aerosols

In pharmaceutical aerosols a drug is dissolved or suspended in a *propellant* (a material that is liquid under the high pressure inside the container but forms a gas under normal atmospheric conditions).

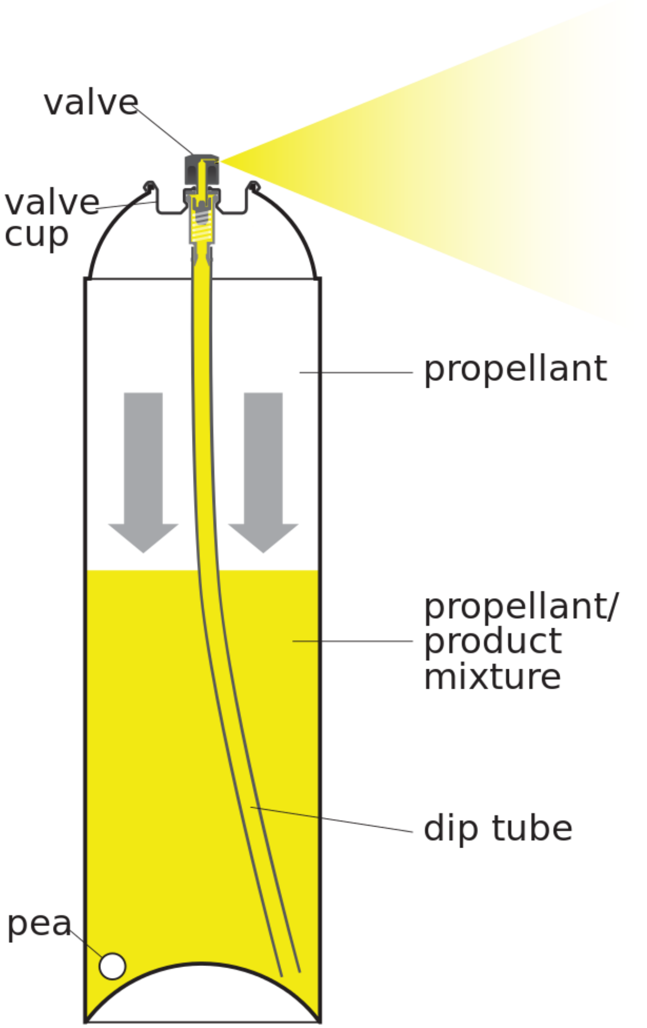
Part of the propellant exists as a gas and exerts the pressure necessary to expel the drug, whereas the remaining exists as liquid and provides a solution or suspension vehicle for the drug.



Liquefaction of gases

Aerosols

- By depressing a valve on the container, some of the drug–propellant mixture is expelled owing to the excess pressure inside the container.
- Outside the container, the liquid propellant reverts to gas and vaporizes off, while the drug forms a fine spray.



Vapor pressure of liquids

Equilibrium vapor pressure

When a liquid is placed in a closed container at a constant temperature, the molecules with the highest energies break away from the surface of the liquid and pass into the gaseous state (evaporate), and some of the molecules subsequently return to the liquid state (condense).

When the rate of condensation equals the rate of vaporization at a definite temperature, the vapor becomes saturated and a dynamic equilibrium is established.

The pressure of the saturated vapor above the liquid is then known as the *equilibrium vapor pressure.*

Vapor pressure of liquids

Clausius–Clapeyron equation

Clausius–Clapeyron equation expresses the relationship between the vapor pressure and the absolute temperature of a liquid:

$$\boldsymbol{ln\frac{P_2}{P_1} = \frac{\Delta H_v(T_2 - T_1)}{RT_1T_2}}$$

$\boldsymbol{P_1}$ and $\boldsymbol{P_2}$: vapor pressures at absolute temperatures $\boldsymbol{T_1}$ and $\boldsymbol{T_2}$.

***ΔHv* :** the *molar heat of vaporization* (the heat absorbed by 1 mole of liquid when it passes into the vapor state).

Vapor pressure of liquids

Clausius–Clapeyron equation: *Example*

Compute the vapor pressure of water at 120°C. The vapor pressure of water at 100°C is 1 atm, and ΔHv is 9720 cal/mole.

$$\boldsymbol{ln\frac{P_2}{P_1} = \frac{\Delta H_v(T_2 - T_1)}{RT_1T_2}}$$

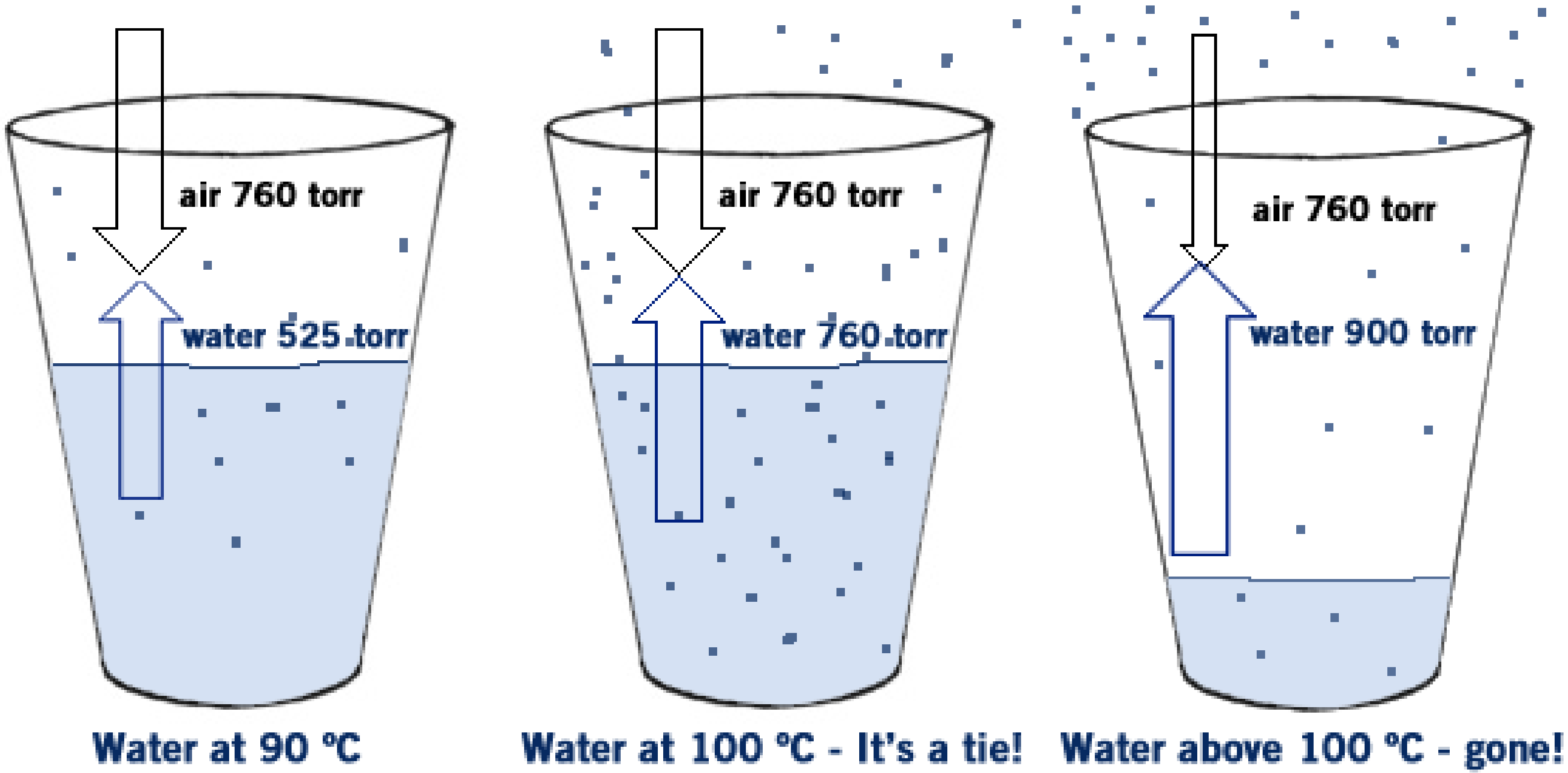
$$\boldsymbol{ln\frac{P_2}{1}} = \frac{9720(393 - 373)}{1.987 \times 393 \times 373}$$

$$\boldsymbol{P_2} = 1.95\ \text{atm}$$

Boiling point

Definition

If a liquid is placed in an open container and heated until the vapor pressure equals the atmospheric pressure, the liquid starts to boil and escape into the gaseous state.

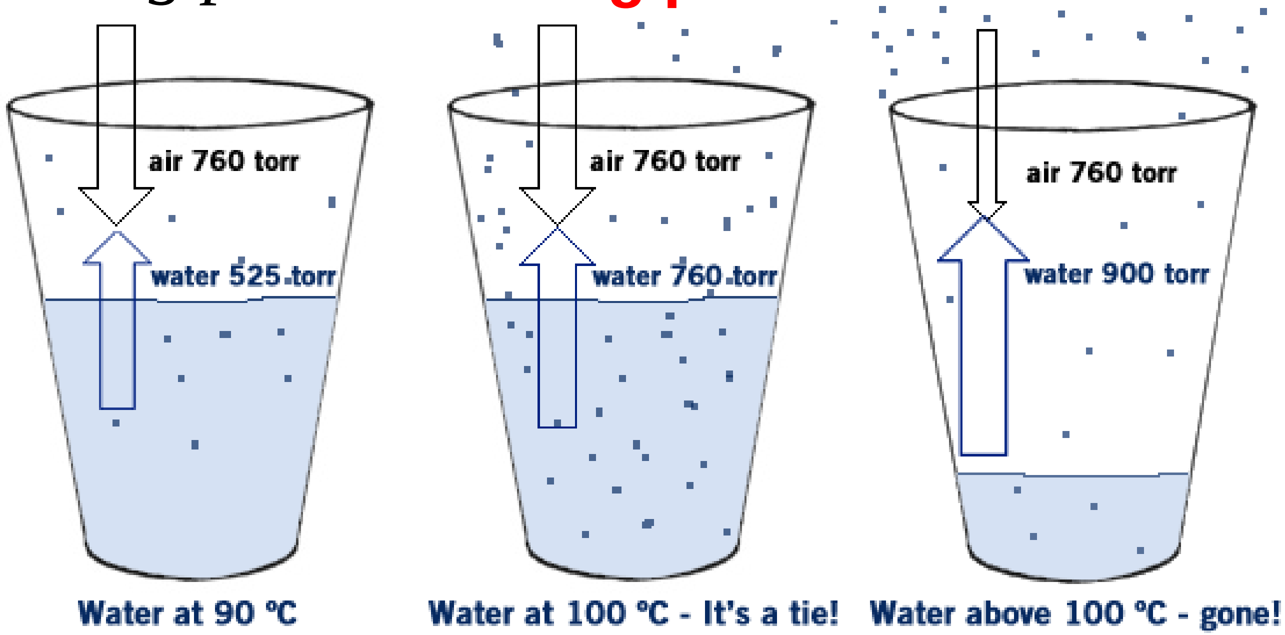


Boiling point

Definition

The temperature at which the vapor pressure of the liquid equals the external or atmospheric pressure is known as the *boiling point.*

Boiling point!



The absorbed heat used to change the liquid to vapor is called the *latent heats of vaporization*.

Boiling point

Clausius–Clapeyron equation

The temperature at which the vapor pressure of the liquid equals an atmospheric pressure of 1 atm is called *normal boiling point* . **(at sea level)**

At higher elevations, the atmospheric pressure decreases and the boiling point is lowered.

At a pressure of 700 mm Hg, water boils at 97.7°C; at 17.5 mm Hg, it boils at 20°C.

The change in boiling point with pressure can be computed by using the Clausius–Clapeyron equation.

Boiling point

Clausius–Clapeyron equation: *Examples*

1. **Determine normal boiling point of chloroform if its heat of vaporization is 31.4 KJ/mol and it has a vapor pressure of 190 mmHg at 25 °C.**
2. **The normal boiling point of benzene is 80.1 °C; at 26.1 °C it has a vapor pressure of 100 mmHg. What is the heat of vaporizartion?**

$$\boldsymbol{ln\frac{P_2}{P_1} = \frac{\Delta H_v(T_2 - T_1)}{RT_1T_2}}$$

Boiling point

Intermolecular forces

The boiling point can be considered the temperature at which thermal agitation can overcome the attractive forces between the molecules of a liquid.

The boiling point of a compound, like the heat of vaporization and the vapor pressure, depends on the magnitude of the attractive forces.

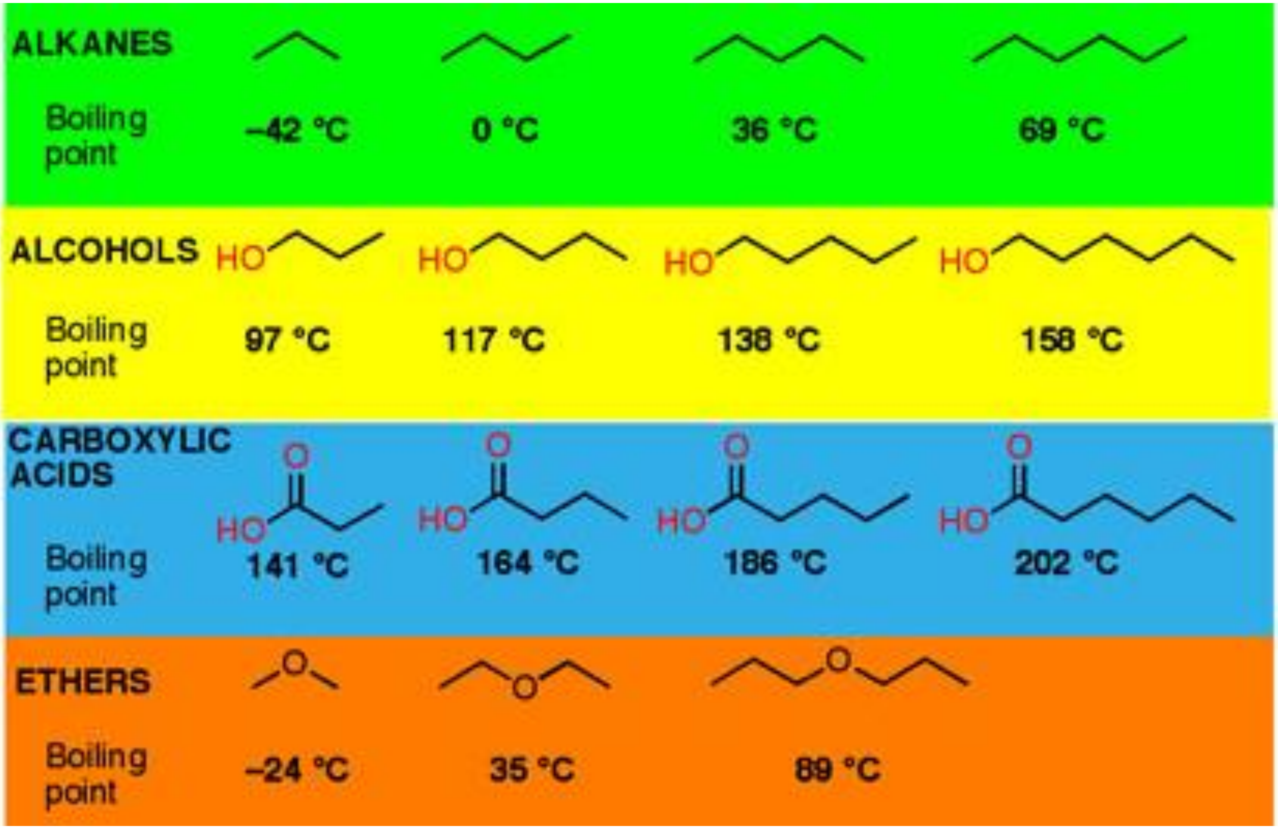
Nonpolar substances have low boiling points and low heats of vaporization because the molecules are held together predominantly by the weak London forces.

Polar molecules (e.g water) exhibit high boiling points and high heats of vaporization because they are associated through hydrogen bonds.

Boiling point

Intermolecular forces

The boiling points of normal hydrocarbons, simple alcohols, and carboxylic acids increase with molecular weight because van der Waals forces become greater with increasing numbers of atoms.

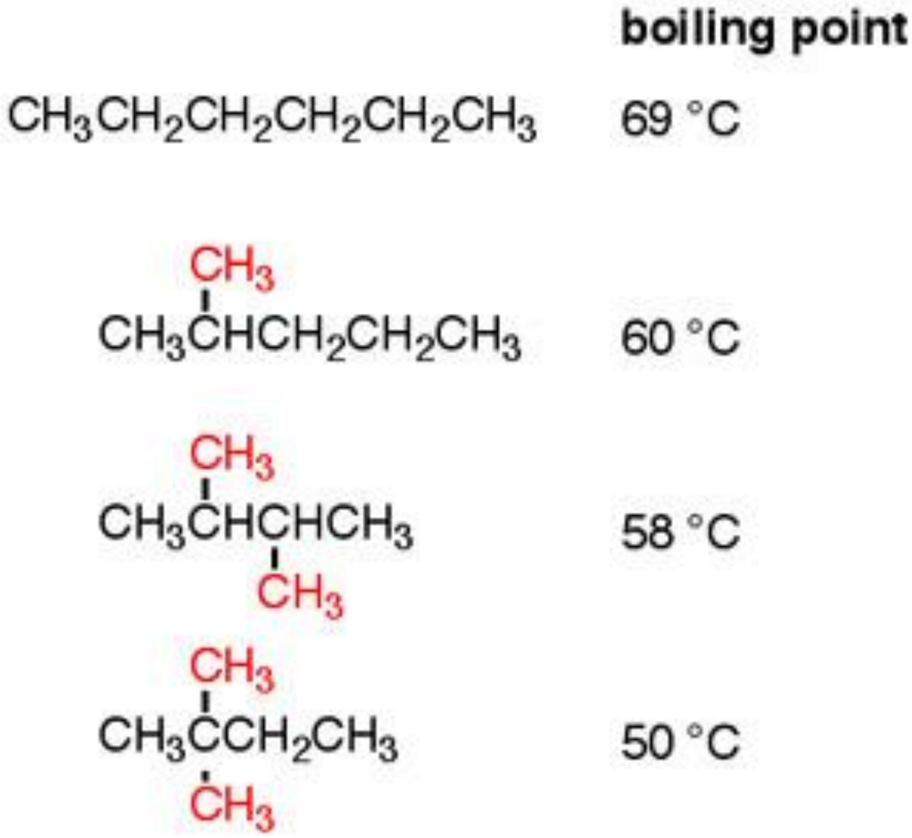


ALKANES				
Boiling point	–42 °C	0 °C	36 °C	69 °C
ALCOHOLS				
Boiling point	97 °C	117 °C	138 °C	158 °C
CARBOXYLIC ACIDS				
Boiling point	141 °C	164 °C	186 °C	202 °C
ETHERS				
Boiling point	–24 °C	35 °C	89 °C	

Boiling point

Intermolecular forces

Branching of the chain produces a less compact molecule with reduced intermolecular attraction, and a decrease in the boiling point.

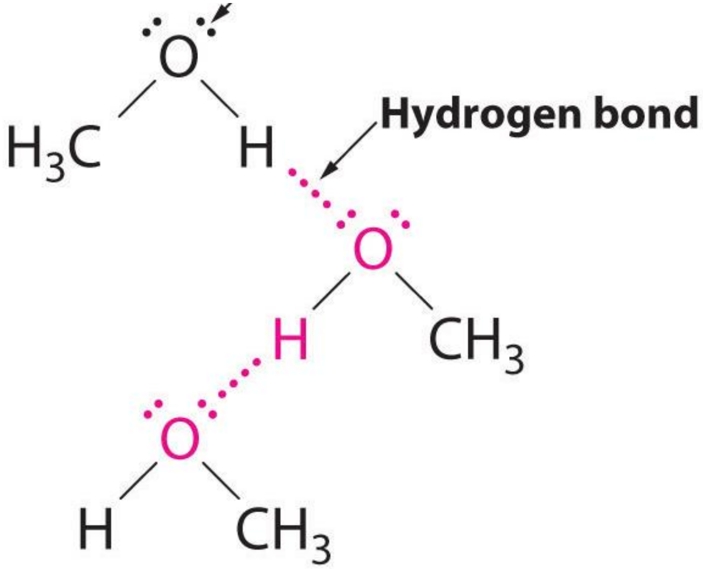


	boiling point
$CH_3CH_2CH_2CH_2CH_2CH_3$	69 °C
$CH_3\overset{\overset{CH_3}{\vert}}{C}HCH_2CH_2CH_3$	60 °C
$CH_3\overset{\overset{CH_3}{\vert}}{C}H\underset{\underset{CH_3}{\vert}}{C}HCH_3$	58 °C
$CH_3\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}CH_2CH_3$	50 °C

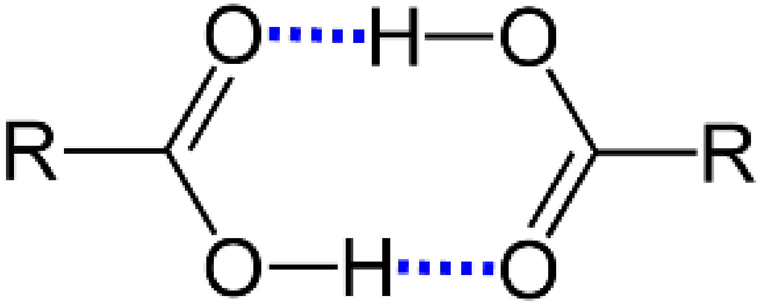
Boiling point

Intermolecular forces

Alcohols boil at a much higher temperature than saturated hydrocarbons of the same molecular weight because of association of the alcohol molecules through hydrogen bonding.



The boiling points of carboxylic acids are higher than that of alcohols because the acids form dimers through hydrogen bonding.



The Solids State

General properties
Crystalline Solids
Amorphous Solids
Melting point

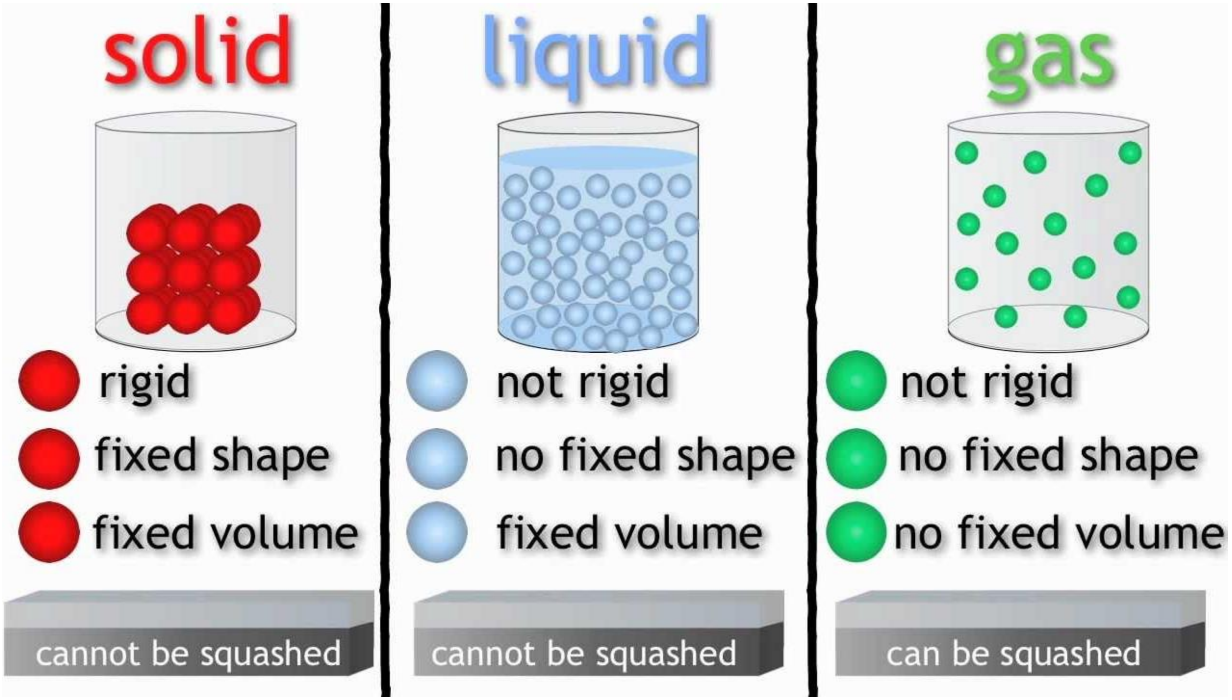
General properties

Solids are much denser than both gases and liquids due to the presence of very strong intermolecular forces.

Solids are essentially incompressible (small empty spaces)

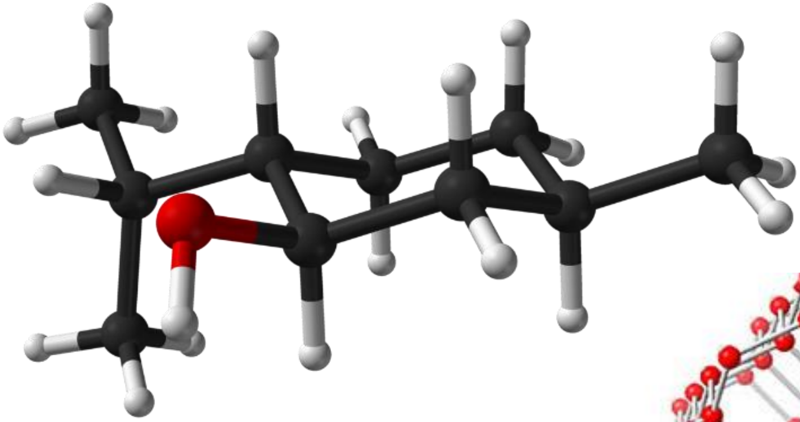
Solids have definite volume and shape (rigid, not fluid)

Solids have no translational motion (only vibration)

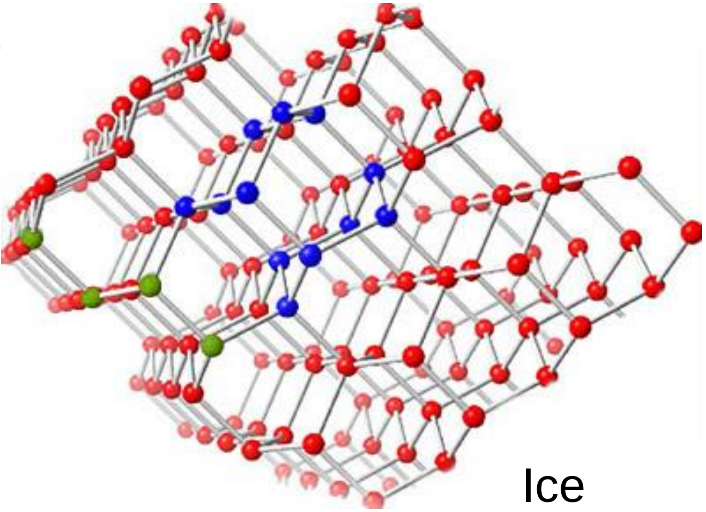


Crystalline Solids

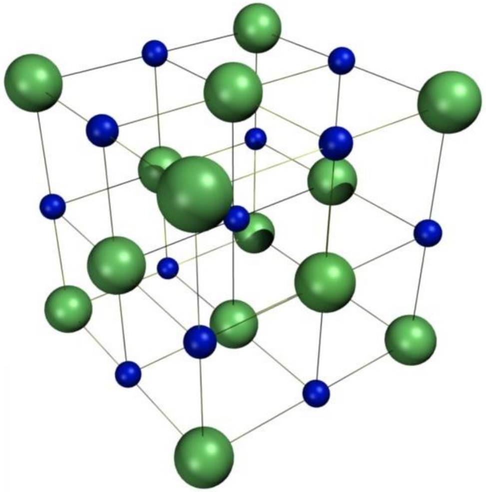
Crystalline solids, such as ice, sodium chloride, and menthol, are composed of structural units arranged in fixed geometric patterns or lattices.



Menthol



Ice



Sodium Chloride

Crystalline Solids

Crystalline solids show definite melting points, passing rather sharply from the solid to the liquid state.

The morphology of a crystalline form is often referred to as its *habit*, where the crystal habit is defined as having the same structure but different outward appearance.

Crystalline Solids

Types of crystalline solids

The units that constitute the crystal structure can be atoms, molecules, or ions

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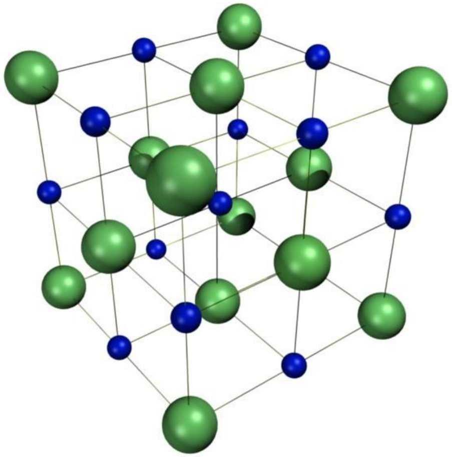
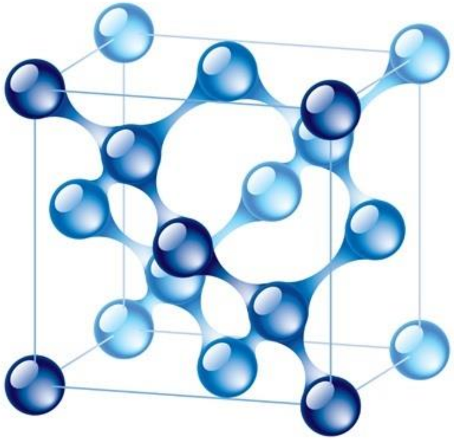


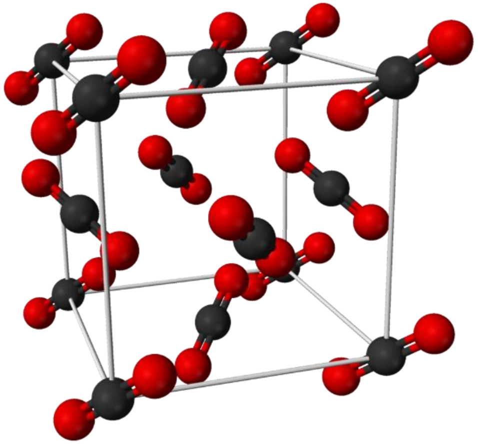
Ionic Solid

Lattice units consist of ions held together by ionic bonds e.g. NaCl



Atomic Solid

Lattice units consist of atoms held together by covalent bonds e.g. diamond



Molecular Solid

Lattice units consists of molecules held together by van der Waals forces e.g. Solid CO_2

Ionic and atomic crystals in general are hard and brittle and have high melting points, while molecular crystals are soft and have relatively low melting points.

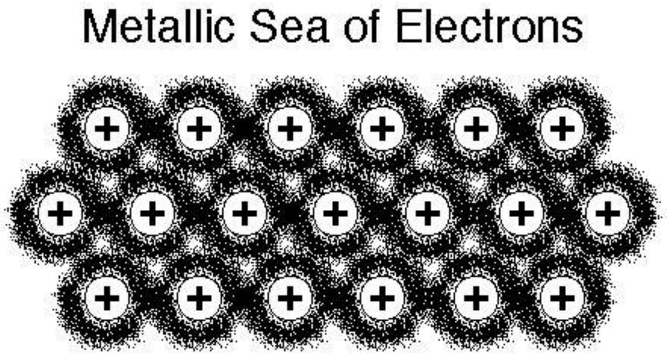
Crystalline Solids

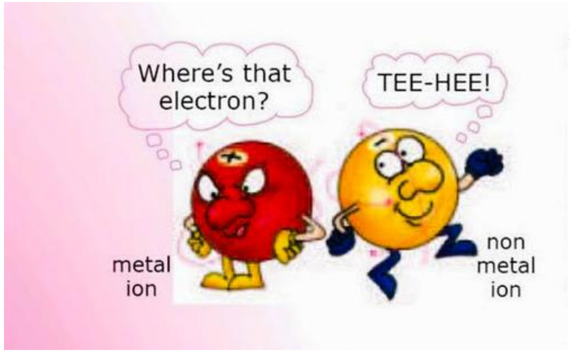
Types of crystalline solids

Metallic crystals are composed of positively charged ions in a field of freely moving electrons. The atoms are held together by metallic bonding.

Metals are good conductors of electricity because of the free movement of the electrons in the lattice.

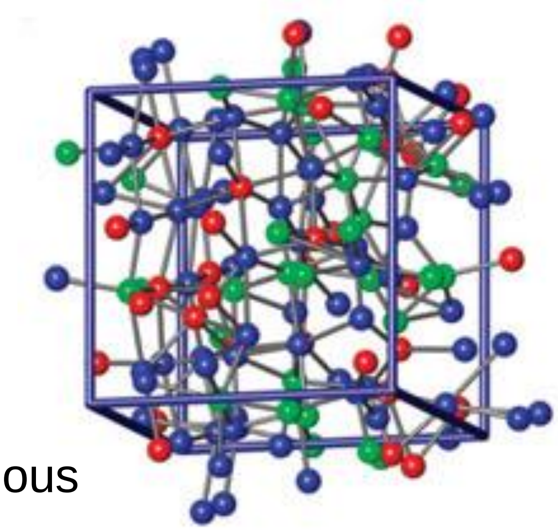
Metals may be soft or hard and have low or high melting points.



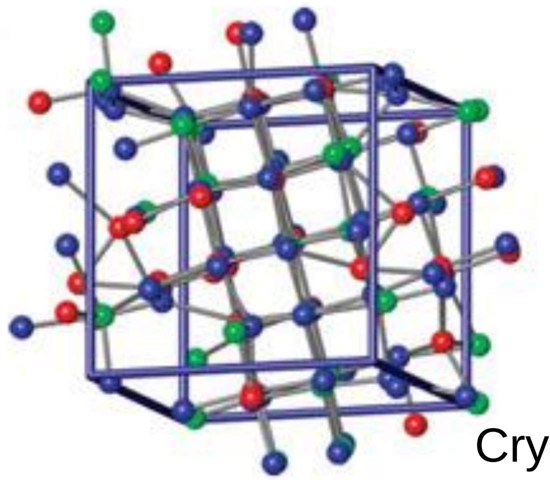


Amorphous Solids

Amorphous solids may be considered as super cooled liquids in which the molecules are arranged in a somewhat random manner as in the liquid state.



Amorphous



Crystalline

They differ from crystalline solids in that they tend to flow when subjected to sufficient pressure over a period of time, and they do not have definite melting points.

Amorphous Solids

The amorphous state is unstable compared to the crystalline solid (it has higher energy than crystalline solid).

The pharmaceutical advantages of amorphous solid is its higher solubility and bioavailability.

Its pharmaceutical disadvantages is its low stability (over time, amorphous solid may transform to the more stable crystalline state).

Melting point

Heat of fusion

The temperature at which a solid passes into liquid state is known as the *melting point*. It is also the *freezing point* of the liquid state of that solid.

The melting point of a pure crystalline solid (or freezing point of a liquid) is the temperature at which the pure liquid and solid exist in equilibrium.

Normal melting or freezing point is the temperature of the equilibrium mixture at an external pressure of 1 atm.

Unlike the boiling point, the melting point is relatively insensitive to pressure because the solid/liquid transition represents only a small change in volume.

Melting point

Heat of fusion

The heat (energy) absorbed when 1 g of a solid melts or the heat liberated when it freezes is known as the *latent heat of fusion.*

$$\frac{\boldsymbol{\Delta T}}{\boldsymbol{\Delta P}} = \boldsymbol{T}\frac{(\boldsymbol{V_l} - \boldsymbol{V_s})}{\boldsymbol{\Delta H_f}}$$

$\boldsymbol{V_l}$ and $\boldsymbol{Vs}$: the molar volumes (cm^3/mole) of the liquid and solid, respectively (Molar volume is computed by dividing the gram molecular weight by the density of the compound).

$\boldsymbol{\Delta H_f}$: the molar heat of fusion (the amount of heat absorbed when 1 mole of the solid changes into liquid)

$\boldsymbol{\Delta T}$: the change of melting point brought about by a pressure change of $\boldsymbol{\Delta P}$.

Melting point

Intermolecular forces

The heat of fusion may be considered as the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting (increased molecular motion) to occur.

A crystal that is bound together by weak forces generally has a low heat of fusion and a low melting point, whereas one bound together by strong forces has a high heat of fusion and a high melting point.

Melting point

Applications

Melting points for organic and inorganic compounds are often used to:

- Characterize organic and inorganic compounds.
- Determine their purity (the melting point of a pure substance is always higher and has a smaller range than the melting point of an impure substance).

Polymorphism

Some elemental substances, such as carbon and sulfur, may exist in more than one crystalline form and are said to be ***allotropic***, which is a special case of polymorphism. Polymorphs have different stabilities and may spontaneously convert from the metastable form at a temperature to the stable form. They also exhibit

1. different melting points.
2. Different x-ray crystal and diffraction patterns
3. different solubilities

Factores affecting polymorphism

The formation of polymorphs of a compound may depend upon several variables relating to the crystallization process, including:

1. solvent differences
2. impurities that may favor a metastable polymorph.
3. the level of supersaturation from which the material is crystallized.
4. the temperature at which the crystallization is carried out;
5. geometry of the covalent bonds.

Polymorphism examples

Perhaps the most common example of polymorphism is the contrast between a diamond and graphite,

both of which are composed of crystalline carbon.

In this case, high pressure and temperature lead to the formation of a diamond from elemental carbon

. It should be noted that a diamond is a less stable (metastable) crystalline form of carbon than is graphite.

Actually, the imperfections in diamonds continue to occur with time very slowly at the low ambient temperature and pressure, into the more stable graphite polymorph

Theobroma oil, or cacao butter, is a polymorphous natural fat. Because it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°C–36°C). Theobroma oil is capable of existing in four polymorphic forms:

1. the unstable gamma form, melting at 18°C;
2. the alpha form, melting at 22°C;
3. the beta prime form, melting at 28°C; and
4. the stable beta form, melting at 34.5°C.

Polymorphism has achieved significance in last decade because different polymorphs exhibit different solubilities.

In the case of slightly soluble drugs, this may affect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug.

AIDS drug ritonavir, which was marketed in a dissolved formulation until a more stable and less soluble polymorph appeared.

This resulted in a voluntary recall and reformulation of the product before it could be reintroduced to the market.

Solvates

Because many pharmaceutical solids are often synthesized by standard organic chemical methods, purified, and then crystallized out of different solvents, residual solvents can be trapped in the crystalline lattice.

This creates a cocrystal, termed a solvate.

The presence of the residual solvent may dramatically affect the crystalline structure of the solid depending on the types of intermolecular interactions that the solvent may have with the crystalline solid.

If the solvent is water then these crystals will termed as hydrates .

Phase Equilibria and the Phase Rule

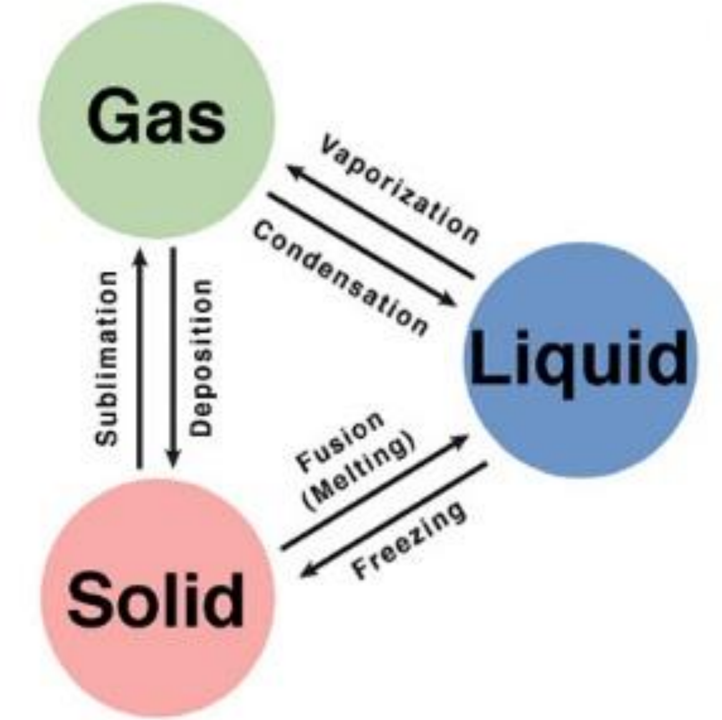
The phase
The phase diagram
The Gibbs phase rule
One component system
Two component system (liquid phases)
Two component system (solid/liquid phases)
Three component systems (liquid phases)

The phase

Definition

A *phase* is the part whose physical and chemical properties are completely equal and homogenous. it is separated from other parts of the system by interfaces.

A system containing water and its vapor is a two-phase system. An equilibrium mixture of ice, liquid water, and water vapor is a three-phase system.



The phase

Definition

A phase may be gas, liquid or solid.

A gas or a gaseous mixture is a single phase.

Completely miscible liquids constitute a single phase.

In an immiscible liquid system, each layer is counted as a separate phase.

Every solid constitutes a single phase except when a solid solution is formed.

A solid solution is considered as a single phase.

Each polymorphic form constitutes a separate phase.

The phase

Examples

How many phases in each of the following systems?

1. **Liquid water, pieces of ice and water vapor are present together.**

Number of phases = 3

2. **Calcium Carbonate undergoes thermal decomposition. $CaCO_3 (s) \rightarrow CaO (s) + CO_2 (g)$**

Number of phases = 3

3. **A solution of NaCl in water**

Number of phases = 1

4. **Liquid water + water vapor**

Number of phases = 2

5. **Liquid water + water vapor + air**

Number of phases = 2

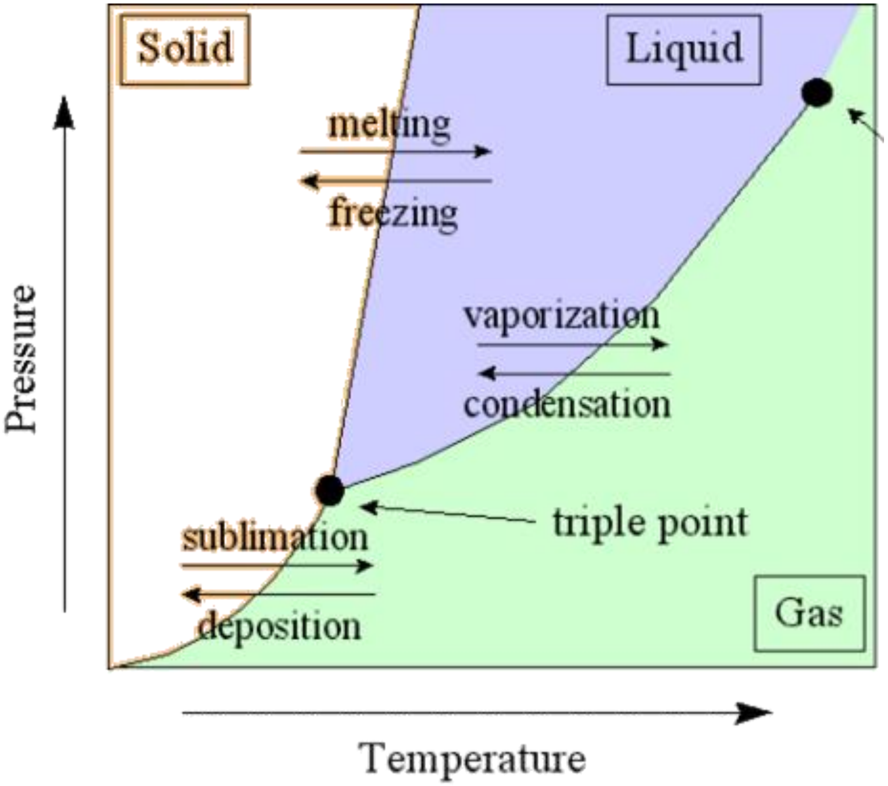
The phase diagram

Phase diagram (also known as *Equilibrium Diagrams*) shows the multisystem state changes with the temperature, pressure, composition and other intensive properties.

The simplest phase diagrams are pressure-temperature diagrams of a single simple substance.

The axes correspond to the pressure and temperature.

The lines in the phase diagram represent two phase systems, while The spaces between the lines represent one phase systems.



The Gibbs phase rule

To understand and define the state of a phase, knowledge of several *independent variables* is required.

Independent variables (also called *Intensive variables*) are the variables that do not depend on the volume or size of the phase, e.g. temperature, pressure, density, boiling point and concentration.

The *Gibbs phase rule* is expressed as follows:

$$\boldsymbol{F = C - P + 2}$$

F is the *number of degrees of freedom* of the system which is the least number of intensive variables required to define the system completely.

C: number of components, ***P***: number of phases present

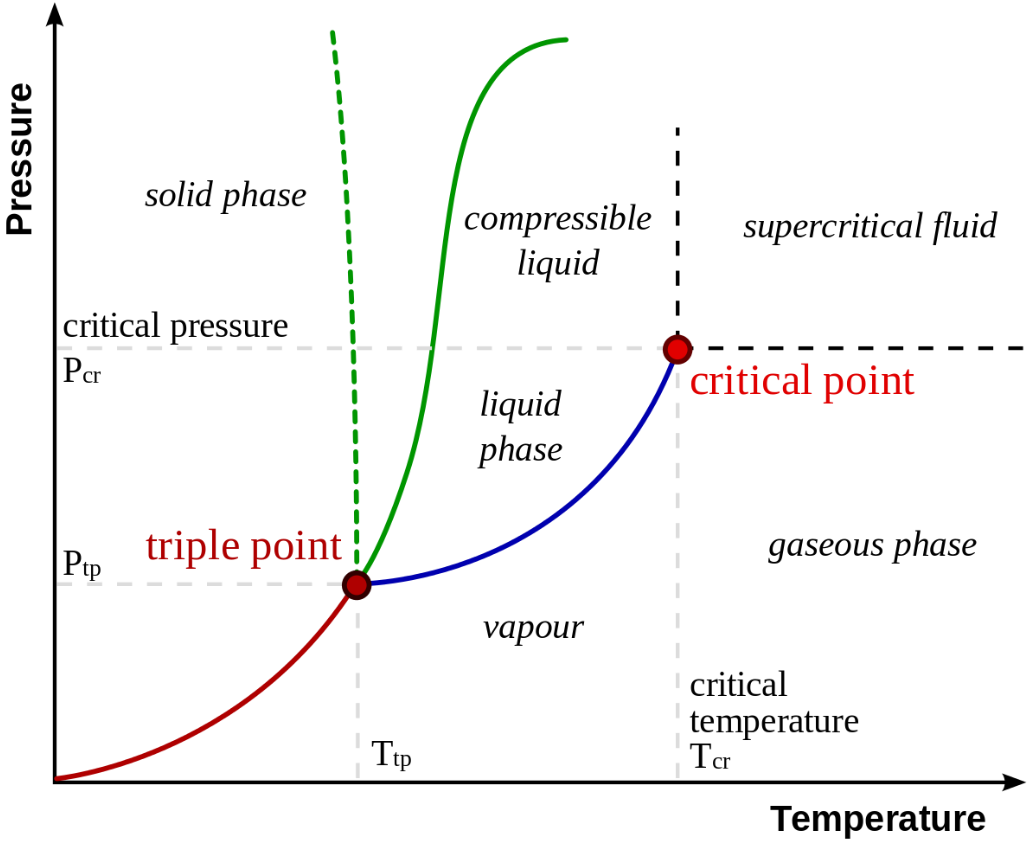
One component system

The Gibbs phase rule

Consider a one component system composed of a liquid with particular volume. Using the phase rule:

F = 1 - 1 + 2 = 2 (the maximum number of degree of freedom for one component system)

Only two independent variables are required to define the system (temperature and pressure)



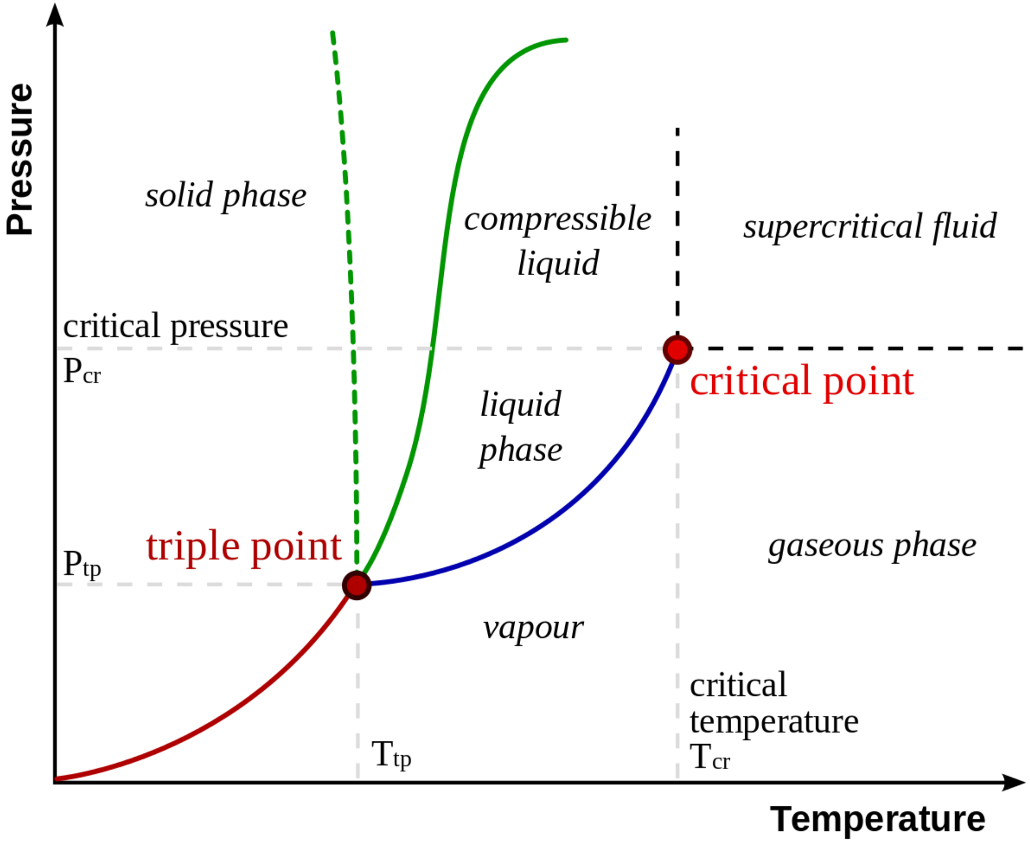
One component system

The Gibbs phase rule

For a one component system comprising a liquid and its vapor. The phase rule states that:

F = 1 - 2 + 2 = 1

Only one independent variable is required to define this system (either temperature or pressure)



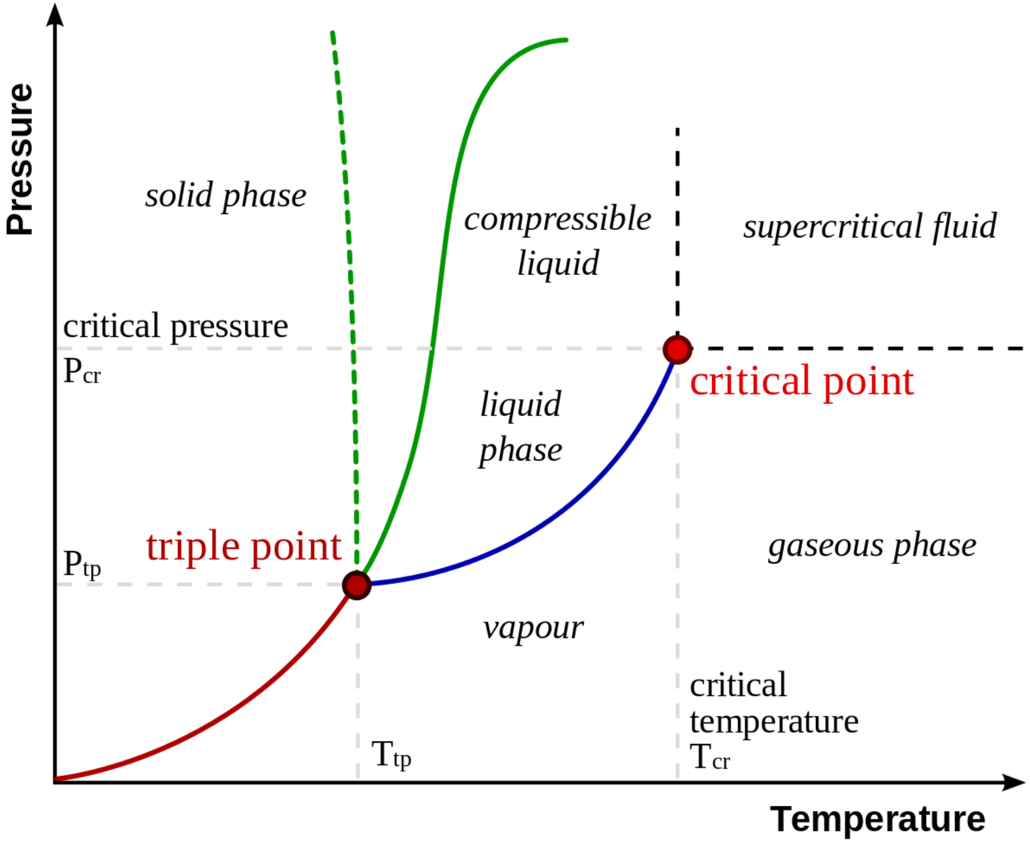
One component system

The Gibbs phase rule

For a one component system composed of solid, liquid, and vapor. The phase rule states that:

F = 1 - 3 + 2 = 0

There are no degrees of freedom. The ice–water–vapor system is completely defined (the temperature and pressure is fixed at a point called the *triple point*).



One component system

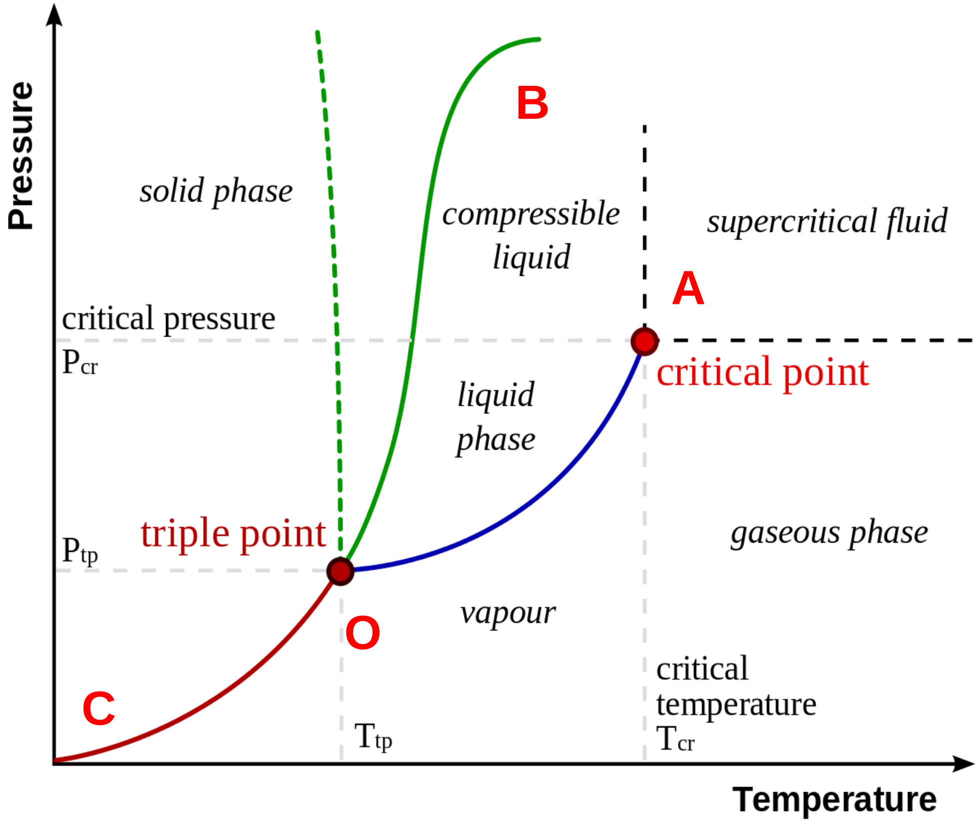
The phase diagram

The curve OA in the phase diagram of one component system represents the vapor pressure curve where vapor and liquid coexist in equilibrium.

The curve OB represents the melting curve where the solid and liquid phases coexist in equilibrium.

The curve OC represents the sublimation curve where the solid and vapor phases coexist in equilibrium.

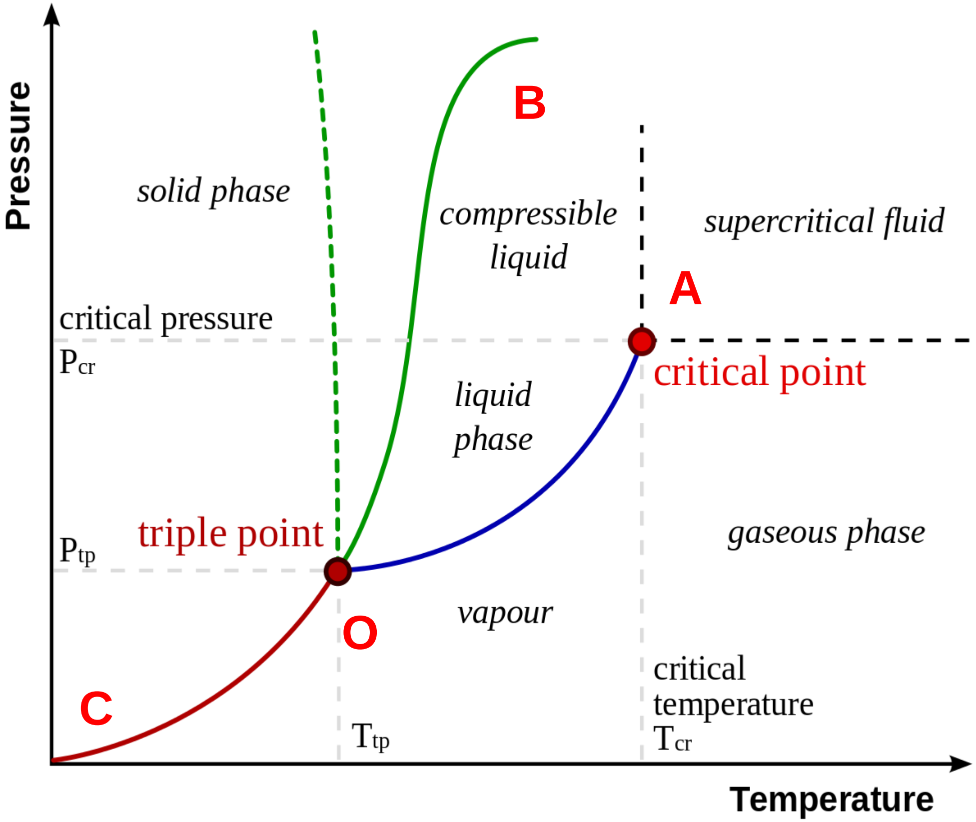
The spaces between the curves represent area of one phase system



One component system

The phase diagram

The *critical point* is the point on a phase diagram that indicates the critical temperature and pressure. While the *triple point* represents the temperature and pressure where all three physical states are in equilibrium.

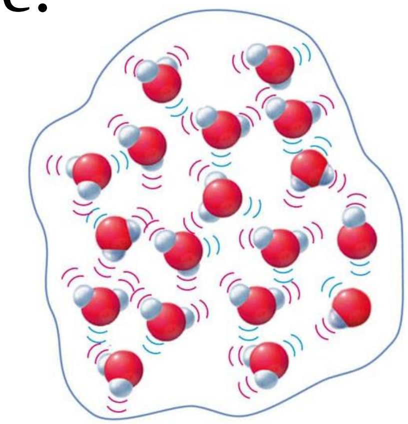


One component system

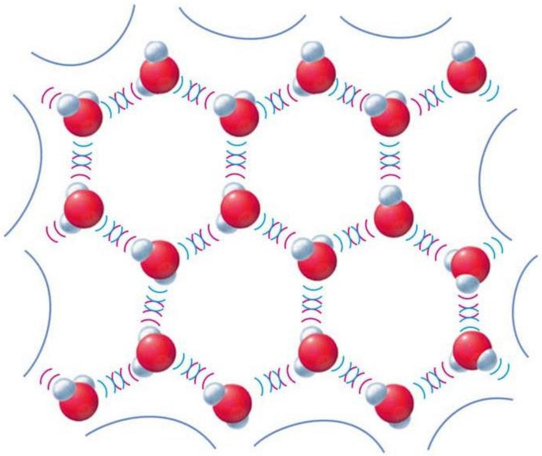
The phase diagram of water

For most substances the solid is denser than the liquid. Therefore; an increase in pressure usually favors the more dense solid phase.

The frozen state of water (ice) is actually less dense than the liquid state. Therefore; increasing pressure (which favors compactness of the molecules) will favor the liquid state.



Liquid water
(dense)



Ice
(less dense)

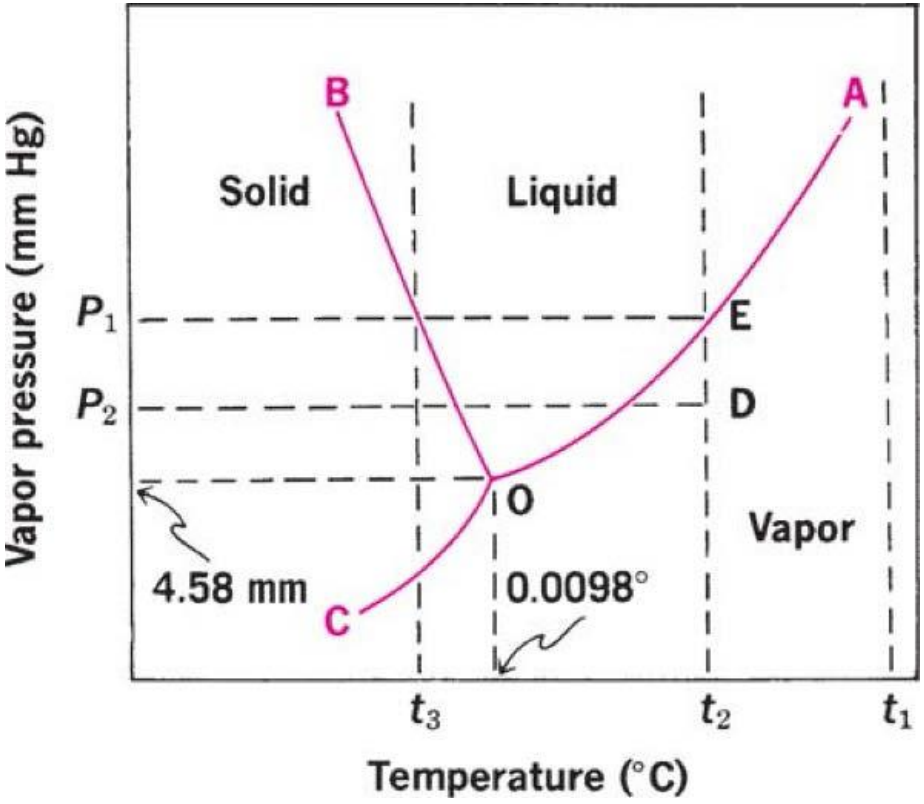
One component system

The phase diagram of water

The melting curve (OB) slopes to the left, unlike most compounds.

The negative slope of OB shows that the freezing point of water decreases with increasing external pressure

At a temperature below the triple point, an increase of pressure on water in the vapor state converts the vapor first to ice and then at higher pressure into liquid water. **Why?**



Two component systems containing liquid phases

Systems containing more than one component are best discussed as *condensed systems*

Condensed systems are systems in which the vapour phase is ignored and only solid and liquid phases are considered.

Systems containing liquids often are classified as

1. Completely immiscible (such as mercury and water) (not concern)
2. Completely miscible in all proportions (e.g. ethanol and water), (solution)
3. Partially miscible (e.g. diethyl ether and water). (considered)

Two component systems containing liquid phases

For two component systems:

C = 2 **F = C – P + 2** ⟹ **F** = 4 – **P**

P = 1 at least, so **F** is 3 at most

Three variables are required: temperature, pressure, and composition.

If the pressure is fixed:

C = 2 **F = C – P +1** ⟹ **F** = 3 **- P**

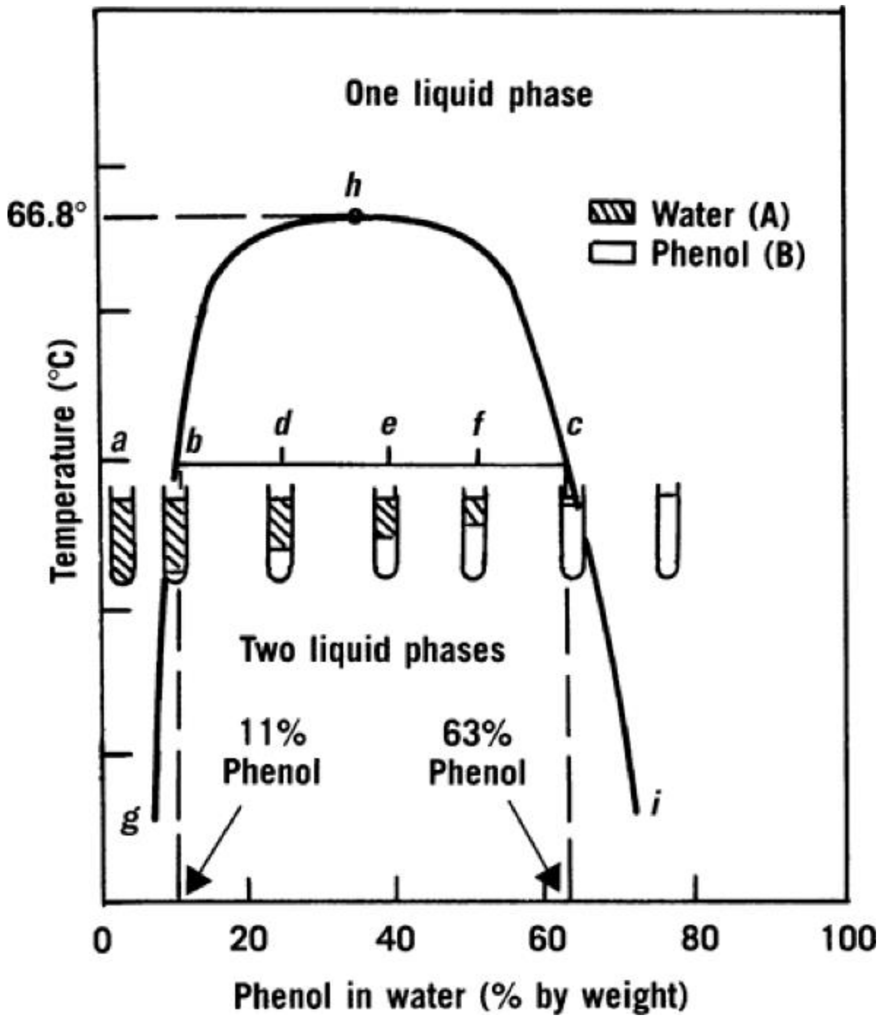
P = 1 at least, so **F** is 2 at most

Only are temperature and composition are required:

Two component systems containing liquid phases

Phase diagrams for two component systems are commonly constructed with temperature and composition as the coordinates.

Usually the composition is expressed as mole fraction or as percent by weight (% w/w). **Why?**



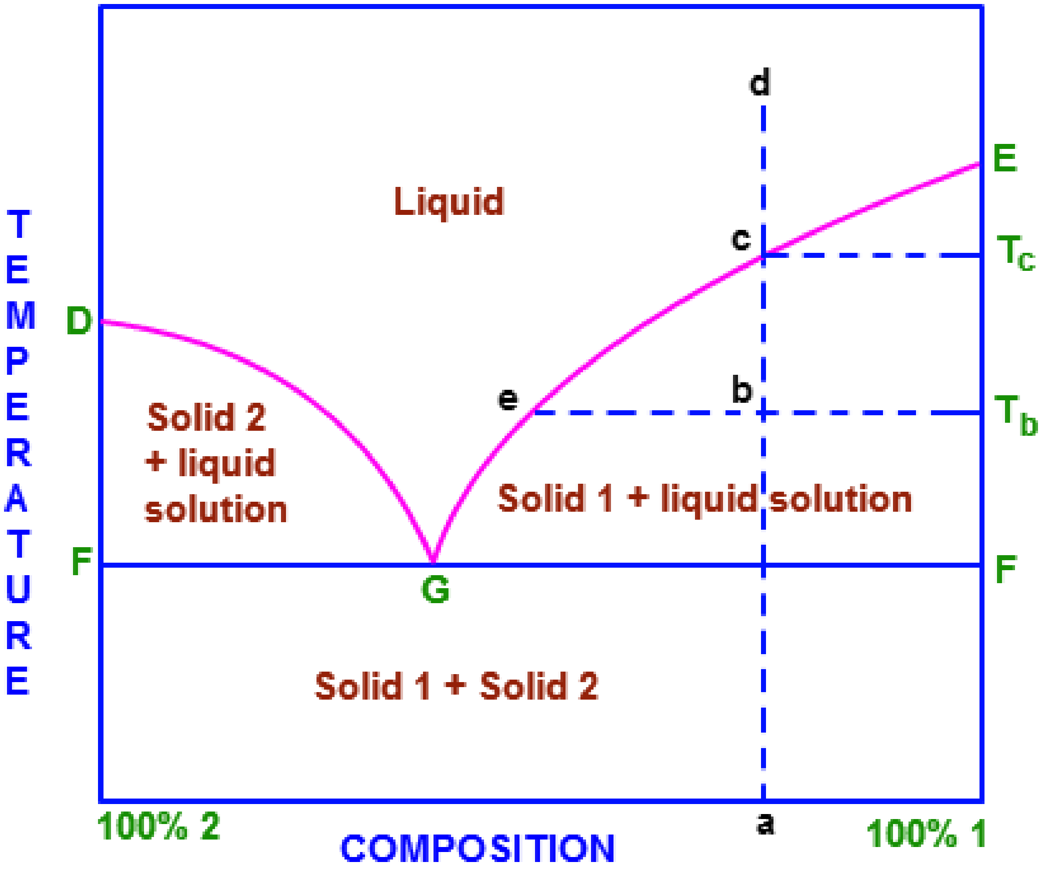
Two component systems containing solid and liquid phases

Two component system consisting of two solids **D** and **E** brought to a temperature above the melting points of both (point **d**).

A one-phase system will form consisting of a liquid solution of **D** and **E**.

The points of **D** and **E** represent the melting points of **D** and **E**.

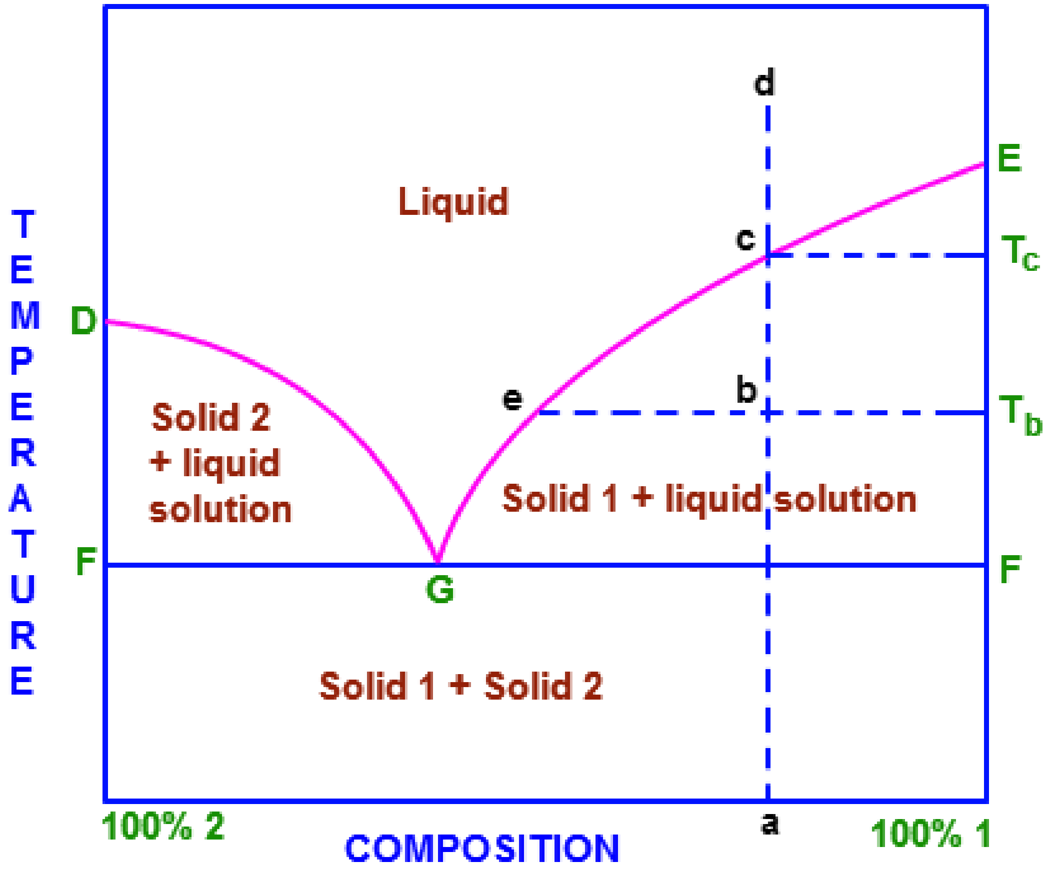
When the temperature fall to point **c**, pure solid **E** will form dispersed in a solution of **D** and **E**.



Two component systems containing solid and liquid phases

At point **G** solid **D**, solid **E** and solution phase are in mutual equilibrium (exist together).

The solid phase at this point is a finely divided two-phase dispersion of crystalline **D** and **E** called a *eutectic*, and **G** is the *eutectic point*. Eutectic melts at a lower temperature than either of its pure components.



Three component system containing liquid phases

For three component systems:

$\mathbf{C} = 3 \quad \mathbf{F = C - P + 2} \Longrightarrow \mathbf{F} = 3 - \mathbf{P} + 2 = 5 - \mathbf{P}$

P = 1 at least, so **F** is 4 at most

Four variables are required: temperature, pressure, and two composition.

If the temperature and pressure is both fixed:

$\mathbf{C} = 3 \quad \mathbf{F = C - P} \Longrightarrow \mathbf{F} = 3 - \mathbf{P}$

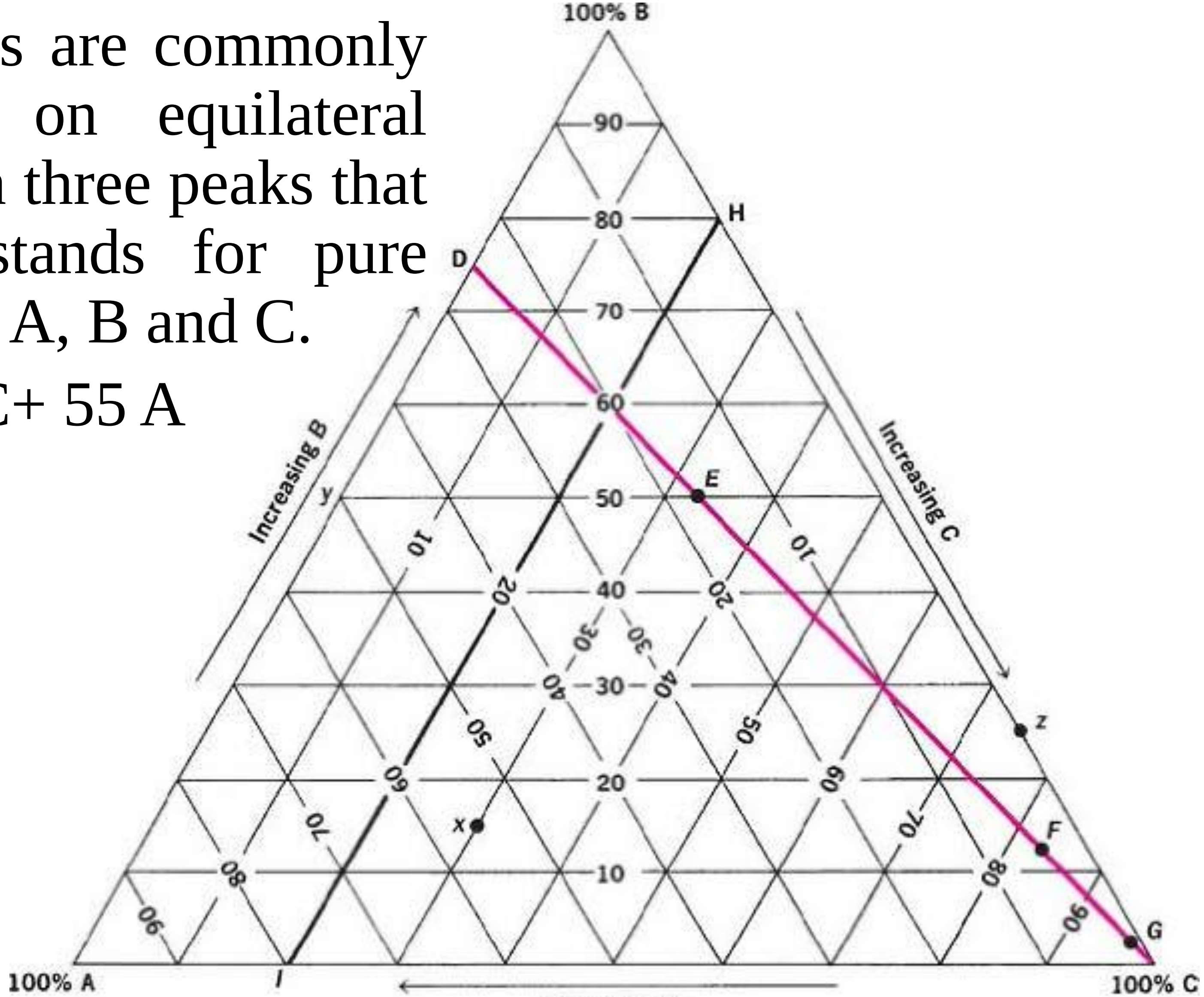
P = 1 at least, so **F** is 2 at most

Only two composition is required.

Three component system containing liquid phases

Phase diagrams are commonly constructed on equilateral triangle with three peaks that separately stands for pure composition A, B and C.

X= 15 B +30 C+ 55 A



Thermal Analysis

Definition
Equipment
Applications

Thermal analysis

Definition

Thermal analysis is a number of methods for observing physical and chemical changes (e.g melting point) of a material upon heating or cooling.

The most common types of thermal analysis are:

- Differntail scanning calorimetry (DSC)
- Differential thermal analysis (DTA),
- Thermogravimetric analysis (TGA)
- Thermomechanical analysis (TMA).

DSC Differntail scanning calorimetry

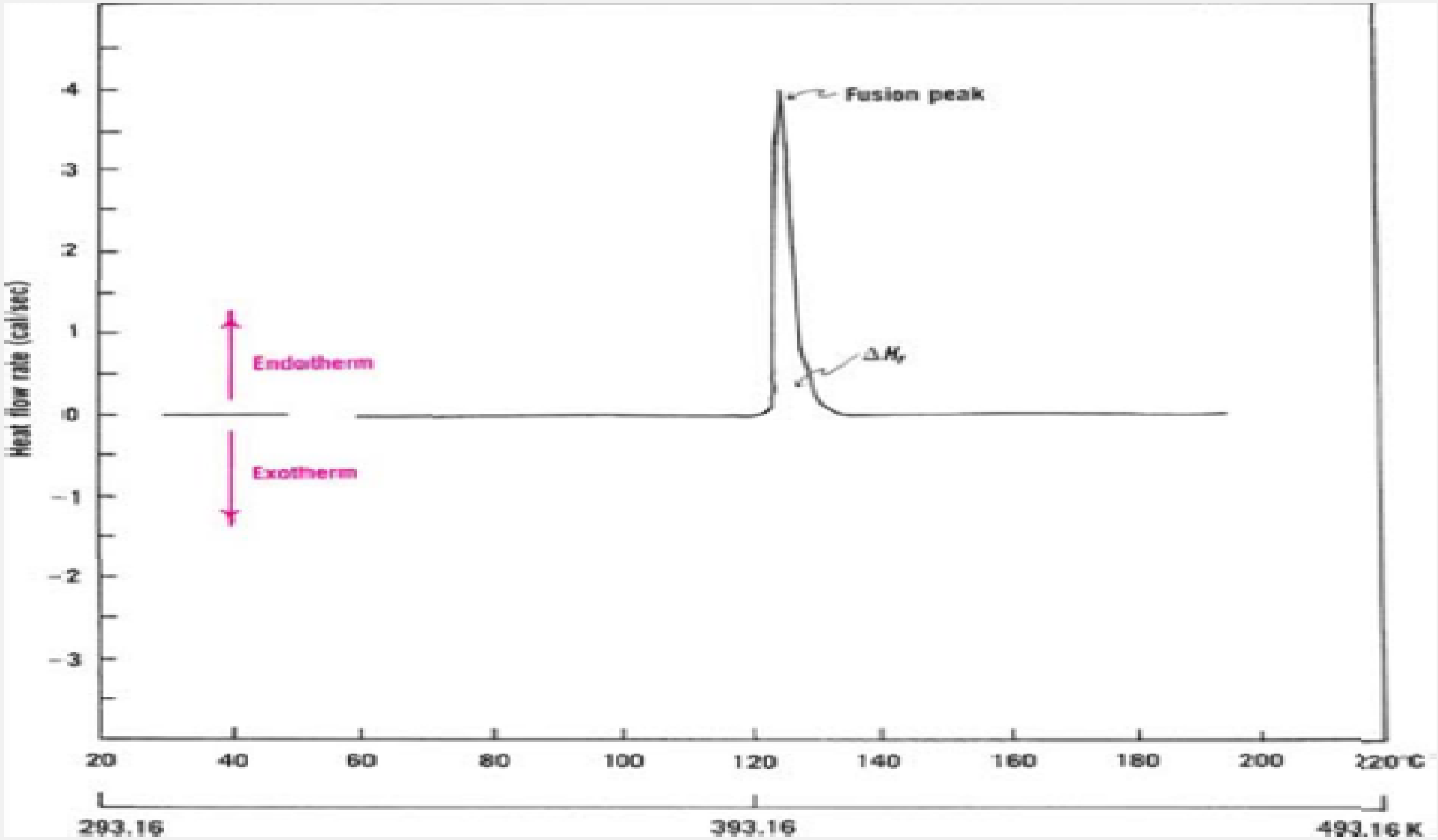


Fig. 2-18. Thermogram of a drug compound. Endothermic transitions (heat absorption) are shown in the upward direction and exothermic transitions (heat loss) are plotted downward. Melting is an endothermic process, whereas crystallization or freezing is an exothermic process. The area of the melting peak is proportional to the heat of fusion, ΔH_f.

Differential scanning calorimetry is a measurement of heat flow into and out of the system. In general, an endothermic (the material is absorbing heat) reaction on a DSC arises from desolvations, melting, glass transitions, and, more rarely, decompositions. An exothermic reaction measured by DSC is usually indicative of a decomposition (energy is released from the bond breaking) process and molecular reorganizations such as crystallization.

Thermal analysis

Applications

Thermal analysis has many applications in pharmaceutical industry and quality control such as:

1. Characterization and identification of compounds.
2. Determination of purity, polymorphism, and stability.
3. Investigation of drug compatibility with excipient(s).

References

Sinko, P. J. M. A. N. 2006. *Martin's physical pharmacy and pharmaceutical sciences: physical chemical and biopharmaceutical principles in the pharmaceutical sciences*, Philadelphia, Lippincott Williams & Wilkins.